PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 19 April 2001 (19.04.01)	
International application No.: PCT/US00/27503	Applicant's or agent's file reference: 7821/JB
International filing date: 05 October 2000 (05.10.00)	Priority date: 08 October 1999 (08.10.99)
Applicant: WU, Shengde et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

05 February 2001 (05.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
7821/JB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 27503	05/10/2000	08/10/1999
Applicant		
THE PROCTER & GAMBLE COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

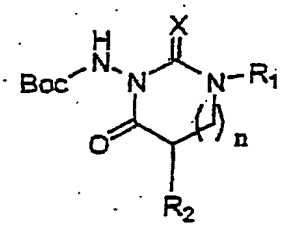
   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention provides a process for the efficient assembly of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils having the following structure:



wherein

X is O or S;
n is 0 or 1;
R_1 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;
R_2 is H, alkyl, carboxyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring; and

when n is 0, R_1 and R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring; or when n is 1, R_1 and the member carbon atom adjacent to the carbon atom containing R_2 may instead together form a ring system; said ring system being carboxyclic ring, heterocyclic ring, or heteroaromatic ring, via a one-pot solution phase or solid phase synthesis from readily available starting materials.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/27503

A. CLASSIFICATION OF SUBJECT MAT[redacted]
IPC 7 C07D233/80 C07D233/86 C07D239/22 C07D401/04 C07D401/06
C07D401/12 C07D403/06 C07D405/06 C07D471/04 C07D513/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YOON J ET AL: "Solution and soluble polymer synthesis of 3-aminoimidazoline-2,4-diones" CHEMICAL COMMUNICATIONS., no. 24, 1998, pages 2703-2704, XP002162268 ROYAL SOCIETY OF CHEMISTRY., GB ISSN: 1359-7345 cited in the application the whole document --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2001	16/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/27503

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SAEGUSA Y ET AL: "Reaction of 1,3,4-Oxadiazolones with Free L-alpha-Amino Acids: A Facile Synthesis of Novel 3,5-Disubstituted Hydantoins " JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 27, no. 3, 1990, pages 739-742, XP000983529 HETEROCORPORATION. PROVO., US ISSN: 0022-152X cited in the application the whole document ---	1
A	VEVERKA M; MARCHALIN M: "Addition-Cyclization Reaction of Ethyl Isothiocyanatoacetate with Carboxylic Acid Hydrazides" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 52, no. 1, 1987, pages 113-119, XP000983448 ACADEMIC PRESS, LONDON., GB ISSN: 0010-0765 page 117, paragraph 5 page 119, paragraph 1 ---	1
A	MURPHY A M ET AL: "Automated Synthesis of Peptide C-Terminal Aldehydes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 114, no. 8, 8 April 1992 (1992-04-08), pages 3156-3157, XP002162269 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 3156, column 2, last paragraph -----	1

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D 3602

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7821/JB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/27503	05/10/2000	08/10/1999
International Patent Classification (IPC) or national classification and IPC C07D233/80		
Applicant THE PROCTER & GAMBLE COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/02/2001	31.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fink, D Telephone No. +49 89 2399 8701

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/27503

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-24 as originally filed

Claims, No.:

1,2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1,2
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The following documents (D) are considered to be relevant:

D1: ..... YOON J. et al.; Chemical Communications, **1998** (24), 2703-2704;
D2: ..... SAEGUSA Y. et al.; Journal of Heterocyclic Chemistry, **27**(3), 739-742, 1990;
D3: ..... VEVERKA M. and MARCHALIN M.; Collection of Czechoslovak Chemical Communications, **52**(1), 113-119 (1987);
D4: ..... MURPHY A. M. et al.; Journal of the American Chemical Society, **114**(8), 3156-3157 (1992);

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1** and **2** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The document **D1** describes (cf., page 2703, scheme 1) a process for the preparation of 3-aminohydantoins by (i) the reaction of N-Boc-hydrazine with N-benzoyloxycarbonyl protected amino acids, (ii) removal of the N-benzoyloxycarbonyl group, (ii) activation of the so obtained free amino group with nitrophenyl chloroformate, (iii) removal of the Boc group and (iv) the cyclization of the so obtained N-*(4-nitrophenoxycarbonyl)glycine hydrazide*.
The present process differs from the process of **D1** in that N-Boc hydrazine is (i) reacted with carbonyl imidazole, the so obtained N-Boc-N'-(imidazol-1-ylcarbonyl)-hydrazine is (ii) coupled with an amino acid ester and the so obtained *1-Boc-4'-(alkoxycarbonylmethyl)semicarbazide* is (iii) cyclized by heating.

The documents **D2** (cf., page 740, scheme II) and **D3** (cf., page 117, fifth paragraph and page 119, first paragraph) disclose the preparation of 3-(*N-acyl*amino)-(thio)hydantoins by the cyclization of an *1-acyl*-4-(alkoxycarbonylmethyl)(thio)semi-carbazide which, in turn, was obtained by reacting *N-acyl*hydrazine with alkoxycarbonylmethyl*iso(thio)cyanate*.

The prior art **D4** does not refer to a process for the preparation of (thio)hydantoins / (thio)dihydro uracils.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application also satisfies the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1** and **2** appears to involve an inventive step (Rule 65(1)(2) PCT):

2.1. Document **D1** - which teaches the preparation of 3-*amino*hydantoin derivatives (cf., the present *N-Boc protected* 3-aminohydantoins) - is considered to represent the **closest prior art**.
The process of **D1** comprises the steps of
(i) reacting N-Boc-hydrazine with N-benzoyloxycarbonyl protected amino acids,
(ii) removing the N-benzoyloxycarbonyl group,
(iii) activating the so obtained free amino group with nitrophenyl chloroformate,
(iv) removing the Boc group, and
(v) cyclizing the so obtained N-*(4-nitrophenoxycarbonyl)glycine hydrazide*.
D1 also teaches the correponding solid phase process.

2.2. The process according to the present **claim 1 differs** from the process of **D1** in that

(i) N-Boc hydrazine is reacted with carbonyl imidazole,
(ii) the so obtained N-Boc-N'-(imidazol-1-ylcarbonyl)hydrazine is coupled with an amino acid ester, and
(iii) the so obtained *1-Boc-4'-(alkoxycarbonylmethyl)semicarbazide* is cyclized by heating.

2.3. In the light of this prior art **D1** the **problem** to be solved by the present application may be seen in the provision of a further process for the preparation of 3-aminohydantoins.

2.4. Accordingly, the present application proposes the processes of the present **claims 1** and **2** in order to solve the given problem.

2.5. It appears that this solution involves an inventive step (Article 33(3) PCT) since none of the available prior art documents suggests a process wherein a *3-(Boc-amino)*hydantoin is prepared via a *one-pot solution phase* or *solid phase synthesis* starting from readily available starting material such as *Boc-hydazine*, *(thio)carbonyldiimidazol* and an *amino acid ester*.
Hence the present solution is regarded to be non-obvious in the light of the available prior art.

2.6. It is therefore considered that the subject-matter of the present **claims 1** and **2** involves an inventive step as set forth in Article 33(3) PCT.

3. MISCELLANEOUS:

3.1. It is noted that the expressions in the claims "alkyl", "carbocyclic ring", "heterocyclic ring", "aromatic ring", "heteroaromatic ring" are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description (Article 6 PCT).

3.2. The explanations of the terms "alkyl", "carbocyclic ring", "heterocyclic ring", and "heteroaromatic ring" as given on pages 2-3 does not correspond with the usual meaning of this term.
The person skilled in the art would not understand the said terms as also referring to *substituted* alkyl groups, carbocyclic rings, heterocyclic rings, and heteroaromatic rings.
Furthermore, the person skilled in the art would not understand the term alkyl as also including *unsaturated* alkyl groups (unsaturated alkyl is "alkenyl" or "alkynyl" rather than "alkyl")
This creates an inconsistency between the claims (cf. the definitions of the groups R_1, R_2 and R) and the description, which leads to a doubt concerning the extent of protection afforded by the claims, thus rendering the claims unclear (Article 6 PCT).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27087 A2

(51) International Patent Classification[7]: C07D 233/00

(21) International Application Number: PCT/US00/27503

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/158,660 8 October 1999 (08.10.1999) US

(71) Applicant *(for all designated States except US)*: **THE PROCTER & GAMBLE COMPANY** [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WU, Shengde** [US/US]; 7563 Lakota Springs Drive, West Chester, OH 45069 (US). **JANUSZ, John, Michael** [US/US]; 7385 Desert Springs Court, West Chester, OH 45069 (US).

(74) Agents: **REED, T., David** et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/27087 A2

(54) Title: PROCESS FOR MAKING BOC-PROTECTED 3-AMINOHYDANTOINS/THIOHYDANTOINS AND 3-AMINODIHYDROURACILS/DIHYDROTHIOURACILS

(57) Abstract: The present invention provides a process for the efficient assembly of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils via a one-pot solution phase or solid phase synthesis from readily available starting materials.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27087 A3

(51) International Patent Classification[7]: C07D 233/80, 233/86, 239/22, 401/04, 401/06, 401/12, 403/06, 405/06, 471/04, 513/04

(21) International Application Number: PCT/US00/27503

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/158,660 8 October 1999 (08.10.1999) US

(71) Applicant *(for all designated States except US)*: **THE PROCTER & GAMBLE COMPANY** [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WU, Shengde** [US/US]; 7563 Lakota Springs Drive, West Chester, OH 45069 (US). **JANUSZ, John, Michael** [US/US]; 7385 Desert Springs Court, West Chester, OH 45069 (US).

(74) Agents: **REED, T., David** et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

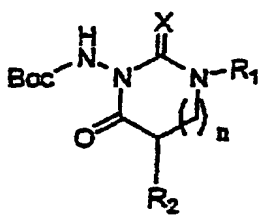
Published:
— *with international search report*

(88) Date of publication of the international search report:
18 October 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/27087 A3

(54) Title: PROCESS FOR MAKING BOC-PROTECTED 3-AMINOHYDANTOINS/THIOHYDANTOINS AND 3-AMINODIHYDROURACILS/DIHYDROTHIOURACILS



(I)

(57) Abstract: The present invention provides a process for the efficient assembly of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils having the following structure: (I) wherein X is O or S; N is 0 or 1; R_1 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring; R_2 is H, alkyl, carboxyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring; and when n is 0, R_1 and R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring; or when n is 1, R_1 and the member carbon atom adjacent to the carbon atom containing R_2 may instead together form a ring system; said ring system being carboxyclic ring, heterocyclic ring, or heteroaromatic ring, via a one-pot solution phase or solid phase synthesis from readily available starting materials.

INTERNATIONAL SEARCH REPORT

Int[redacted]al Application No
PCT/US 00/27503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/80 C07D233/86 C07D239/22 C07D401/04 C07D401/06
C07D401/12 C07D403/06 C07D405/06 C07D471/04 C07D513/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YOON J ET AL: "Solution and soluble polymer synthesis of 3-aminoimidazoline-2,4-diones" CHEMICAL COMMUNICATIONS., no. 24, 1998, pages 2703-2704, XP002162268 ROYAL SOCIETY OF CHEMISTRY., GB ISSN: 1359-7345 cited in the application the whole document --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2001	16/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte[redacted]al Application No
PC[redacted] 00/27503

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SAEGUSA Y ET AL: "Reaction of 1,3,4-Oxadiazolones with Free L-alpha-Amino Acids: A Facile Synthesis of Novel 3,5-Disubstituted Hydantoins " JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 27, no. 3, 1990, pages 739-742, XP000983529 HETEROCORPORATION. PROVO., US ISSN: 0022-152X cited in the application the whole document	1
A	VEVERKA M; MARCHALIN M: "Addition-Cyclization Reaction of Ethyl Isothiocyanatoacetate with Carboxylic Acid Hydrazides" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 52, no. 1, 1987, pages 113-119, XP000983448 ACADEMIC PRESS, LONDON., GB ISSN: 0010-0765 page 117, paragraph 5 page 119, paragraph 1	1
A	MURPHY A M ET AL: "Automated Synthesis of Peptide C-Terminal Aldehydes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 114, no. 8, 8 April 1992 (1992-04-08), pages 3156-3157, XP002162269 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 3156, column 2, last paragraph	1

1

PROCESS FOR MAKING BOC-PROTECTED 3-AMINOHYDANTOINS/THIOHYDANTOINS AND 3-AMINODIHYDROURACILS/DIHYDROTHIOURACILS

Technical Field

The present invention is directed to a process for the efficient solution and solid-phase synthesis of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils.

Background of the Invention

The present invention is directed to a novel process for synthesizing Boc-protected 3-aminohydantoins, 3-aminodihydrouracils, and their thio-substituted counterparts using a one-pot solution-phase or solid-phase process. 3-aminohydantoin and 3-aminodihydrouracil derivatives are useful in both the pharmaceutical and agrochemical industries. For example, compounds containing the 3-aminohydantoin or 3-aminodihydrouracil nucleus are useful as anticonvulsant agents, antibacterial agents, metalloprotease inhibitors, diuretic agents, and pesticides.

Synthetic routes for the preparation of 3-aminohydantoin derivatives are disclosed in the following references: Kiec-Kononowicz, K.; Zejc, A.; Byrtus, H. *Pol. J. Chem.* **1984**, *58*, 585. Lange, J. *et al. Polish Patent*, PL 123138 B1, April 30, **1984**. Wright, G. C.; Michels, J. G.; Spencer, C. F. *J. Med. Chem.* **1969**, *12*, 379-381. Bernard, L. *et al. French Patent*, 2000801, January 24, **1969**. Kobayashi, N. et al. *Japanese Patent*, 09176131 A2, July 8, **1997**. Taub, W. *U.S. Patent* 2767193, **1956**. *Chem. Abstr.*, **1957**, *51*, 5811. Szczepanski, H.; Kristinsson, H.; Maienfish, P.; Ehrenfreund, J. WO 95/18123, **1995**. Lindemann, A.; Khan, N. H.; Hofmann, K. *J. Am. Chem. Soc.*, **1952**, *74*, 476-479. Gante, J.; Lautsch, W. *Chem. Ber.*, **1964**, *97*, 994. Schlogl, K.; Derkosch, J.; Korger, G. C. *Monatsh. Chem.* **1954**, *85*, 607. Schlogl, K.; Korger, G. *Monatsh. Chem.* **1951**, *82*, 799. Davidson, J. S. *J. Chem. Soc.* **1964**, 4646-4647. Gillis, B. T.; Dain, J. G. *J. Heterocyclic Chem.* **1971**, *8*, 339-339. Wildonger, R. A.; Winstead, M. B. *J. Heterocyclic Chem.* **1967**, *4*, 981-982. Lalezari, I. *J. Heterocyclic Chem.* **1985**, *22*, 741-743. Saegusa, Y.; Harada, S.; Nakamura, S. *J. Heterocyclic Chem.* **1990**, *27*, 739-742. Milcent, R.; Akhnazarian, A.; Lensen, N. *J. Heterocyclic Chem.* **1996**, *33*, 1829-1833. Ragab, F. A.; Eid, N. M.; El-Tawab, H. A. *Pharmazie* **1997**, *52* (12), 926-929. Yoon, J; Cho, C-W; Han; H; Janda, K. D. *Chem. Comm.* **1998**, 2703-2704. However, in general the synthetic routes disclosed above involve multiple steps, require harsh reaction conditions, and/or produce relatively low yields.

Additionally, there has been growing interest in the development of solid-phase synthetic approaches to hydantoin and dihydrouracil derivatives, particularly those substituted at the *N*-1, *N*-3, and C-5 positions. Syntheses of 1-aminohydantoins and 3-aminohydantoins by solid-phase synthetic approaches are disclosed in the following references: Dewitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci.* **1993**, *90*, 6909-6913. Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937-940. Hanessisan, S.; Yany, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5835-5838. Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603-4606. Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090-6092. Gong, Y-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081-3086. Xiao, X.; Ngu, K.; Chao, C.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 6968-6973. Smith, J.; Liras, J. L.; Schneider, S. E.; Anslyn, E. V. J. *J. Org. Chem.* **1996**, *61*, 8811-8813. Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230-3233. Wilson, L. J.; Li, M.; Portlock, D. E. *Tetrahedron Lett.* **1998**, *39*, 5135-5138. Hamuro, Y.; Marshall, W. J.; Scialdone, M. A. *J. Comb. Chem.* **1999**, *1*, 163-167.

There is a continuing need for improved processes for producing 3-aminohydantoins, 3-aminodihydrouracils, and their thio-substituted counterparts.

Summary of the Invention

The present invention provides a process for the efficient assembly of Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils via a one-pot solution phase or solid phase synthesis from readily available starting materials.

Detailed Description of the Invention

Definitions and Usage of Terms

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Alkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified.

"Aromatic ring" is a benzene ring or a naphthlene ring.

"Carbocyclic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic rings are not aromatic. Carbocyclic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6

carbon atoms in the ring. Bicyclic carbocyclic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms. As used herein, halogens are not heteroatoms.

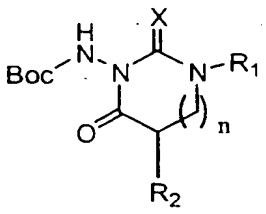
"Heterocyclic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring. Heterocyclic rings are not aromatic. Heterocyclic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Bicyclic heteroaromatic rings are ring systems wherein at least one of the two rings is a heteroaromatic ring and the other ring is a heteroaromatic ring, an aromatic ring, a carbocyclic ring, or a heterocyclic ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring.

"Member atom" refers to a polyvalent atom (C, O, N, or S atom) in a chain or ring system that continues the chain or ring system. For example, in benzene the six carbon atoms are member atoms and the six hydrogen atoms are not member atoms.

Compounds Prepared Using the Present Process

The present invention is directed to a one-pot, solution-phase process for making Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils according to **Formula I** below:



Formula I

In **Formula I** above, X is O or S.

In **Formula I** above, n is 0 or 1.

In **Formula I** above, R_1 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring. When R_1 is substituted alkyl, preferred substituents include: halo, hydroxy, alkoxy, aryloxy, acyloxy, carboxy, mercapto, alkylthio, arylthio, acylthio, carbamoyl, amido, aromatic ring, heteroaromatic ring, carbocyclic ring, and heterocyclic ring.

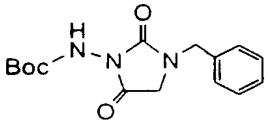
In **Formula I** above, R_2 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring. When R_2 is substituted alkyl, preferred substituents include: halo, hydroxy, alkoxy, aryloxy, acyloxy, carboxy, alkoxycarbonyl, mercapto, alkylthio, arylthio, acylthio, amino, carbamoyl, carbamoyloxy, amido, alkoxylamido, ureido, guanidino, aryl, heteroaryl, cycloalkyl or heterocyclyl.

In **Formula I** above, when n is 0, R_1 and R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring. When n is 1, R_1 and the member carbon atom adjacent to the carbon atom containing R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring.

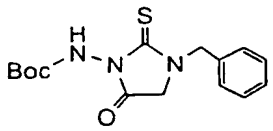
The Boc-protected 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils of the present invention may be further modified into substituted 3-aminohydantoins/thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils using methods known to one of ordinary skill in the art.

Compounds which may be prepared using the present invention include, but are not limited to the following:

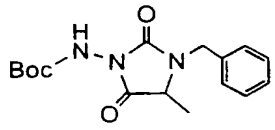
Carbamic acid, [2,5-dioxo-3-(phenylmethyl)-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



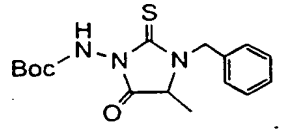
Carbamic acid, [5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



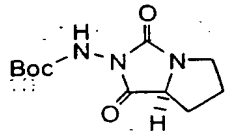
Carbamic acid, [4-methyl-2,5-dioxo-3-(phenylmethyl)-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



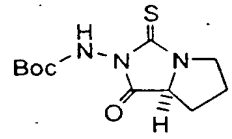
Carbamic acid, [4-methyl-5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



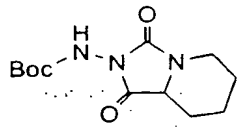
Carbamic acid, ((7aS)-tetrahydro-1,3-dioxo-1*H*-pyrrolo[1,2-c]imidazol-2(3*H*)-yl-, 1,1-dimethylethyl ester.



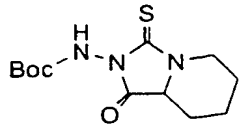
Carbamic acid, ((7aS)-tetrahydro-1-oxo-3-thioxo-1*H*-pyrrolo[1,2-c]imidazol-2(3*H*)-yl-, 1,1-dimethylethyl ester.



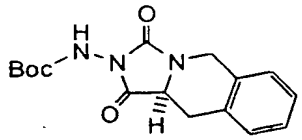
Carbamic acid, (Hexahydro-1,3-dioxoimidazol[1,5-a]pyridin-2(3*H*)-yl)-, 1,1-dimethylethyl ester.



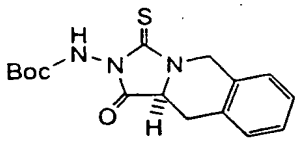
Carbamic acid, (Hexahydro-1-oxo-3-thioxoimidazol[1,5-a]pyridin-2(3*H*)-yl)-, 1,1-dimethylethyl ester.



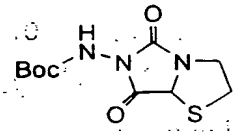
Carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1,3-dioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester.



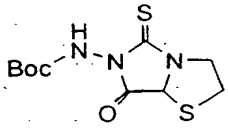
Carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1-oxo-3-thioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester.



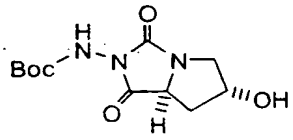
Carbamic acid, (Tetrahydro-5,7-dioxoimidazol[5,1-b]thiazol-6(5*H*)-yl)-, 1,1-dimethylethyl ester.



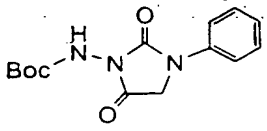
Carbamic acid, (Tetrahydro-7-oxo-7-thioxoimidazol[5,1-b]thiazol-6(5*H*)-yl)-, 1,1-dimethylethyl ester.



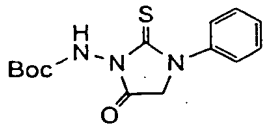
Carbamic acid, ((6*R*,7aS)-tetrahydro-6-hydroxy-1,3-dioxo-1*H*-pyrrolo[1,2-c]imidazol-2(3*H*)-yl-, 1,1-dimethylethyl ester.



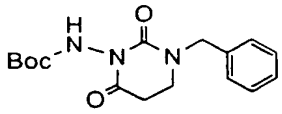
Carbamic acid, (2,5-dioxo-3-phenyl-1-imidazolidinyl)-, 1,1-dimethylethyl ester.



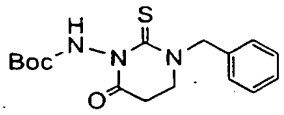
Carbamic acid, (5-oxo-3-phenyl-2-thioxo-1-imidazolidinyl)-, 1,1-dimethylethyl ester.



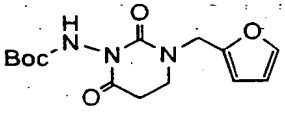
Carbamic acid, (tetrahydro-2,6-dioxo-3-(phenylmethyl)-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



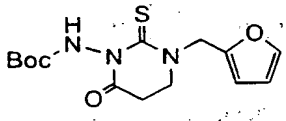
Carbamic acid, (tetrahydro-6-oxo-3-(phenylmethyl)-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



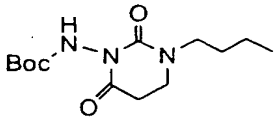
Carbamic acid, (3-(2-furanylmethyl)tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



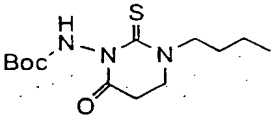
Carbamic acid, (3-(2-furanylmethyl)tetrahydro-6-oxo-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



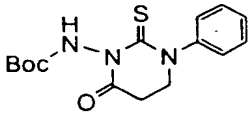
Carbamic acid, (3-butyltetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



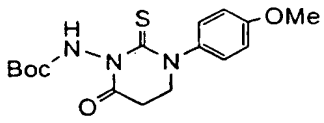
Carbamic acid, (3-butyltetrahydro-6-oxo-2-thioxo-1(2*H*)-pyrimidinyl)-,1,1-dimethylethyl ester.



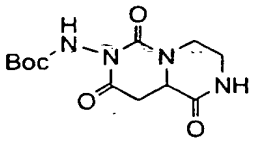
Carbamic acid, (tetrahydro-6-oxo-3-phenyl-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



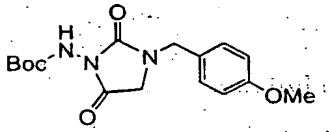
Carbamic acid, (tetrahydro-6-oxo-3-(4-methoxyphenyl)-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester.



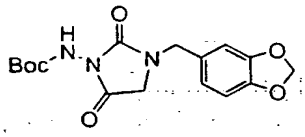
Carbamic acid, (hexahydro-1,6,8-trioxo-2*H*-pyrazinol[1,2-c]pyrimidin-7(6*H*)- yl)-, 1,1-dimethylethyl ester.



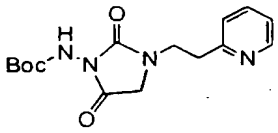
Carbamic acid, [3-[(4-methoxyphenyl)methyl)-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



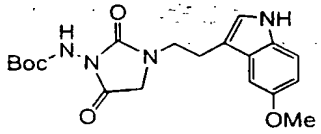
Carbamic acid, [3-(1,3-benzodioxol-5-ylmethyl)-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



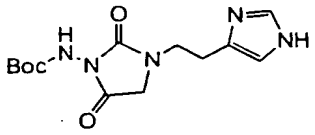
Carbamic acid, [2,5-dioxo-3-[2-(2-pyridinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



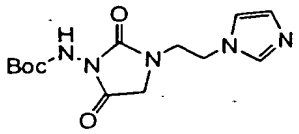
Carbamic acid, [3-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-2,5-dioxo-1-imidazolidinyl]- 1,1-dimethylethyl ester.



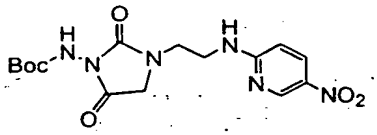
Carbamic acid, [3-[2-(1*H*-imidazol-4-yl)-ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



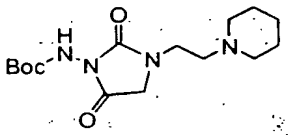
Carbamic acid, [3-[2-(1*H*-imidazol-1-yl)-ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



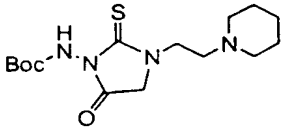
Carbamic acid, [3-[2-[[5-nitro-2-pyridinyl]amino]ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



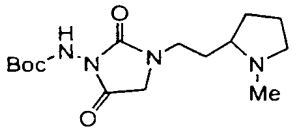
Carbamic acid, [2,5-dioxo-3-[2-(1-piperidinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



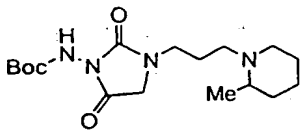
Carbamic acid, [5-oxo-3-[2-(1- piperidinyl)ethyl]-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



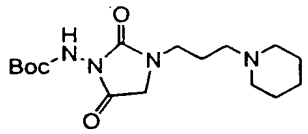
Carbamic acid, [3-[2-(1-methyl-2-pyrrolidinyl)ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



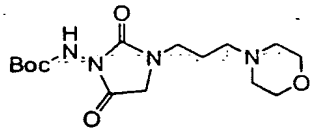
Carbamic acid, [3-[2-(2-methyl-1-piperidinyl)propyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



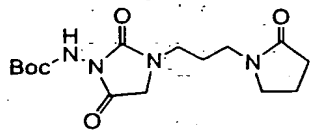
Carbamic acid, [2,5-dioxo-3-[3-(1-piperidinyl)propyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



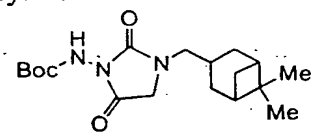
Carbamic acid, [3-[3-(4-morpholinyl)propyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



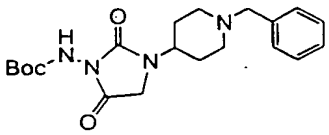
Carbamic acid, [2,5-dioxo-3-[3-(2-oxo-1-pyrrolidinyl)propyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



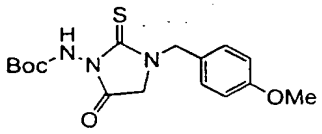
Carbamic acid, [3-[(6,6-dimethylbicyclo[3.1.1]hept-3-yl)methyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



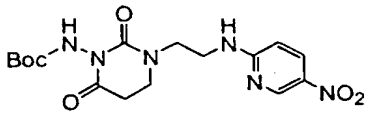
Carbamic acid, [2,5-dioxo-3-[1-(phenylmethyl)-4-piperidinyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



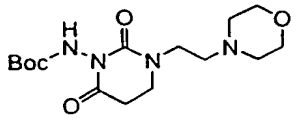
Carbamic acid, [3-[(4-methoxyphenyl)methyl)-5-oxo-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester.



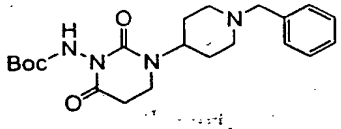
Carbamic acid, [tetrahydro-3-[(5-nitro-2-pyridinyl)amino]ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester.



Carbamic acid, [tetrahydro-3-[2-(4-morpholinyl)ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester.



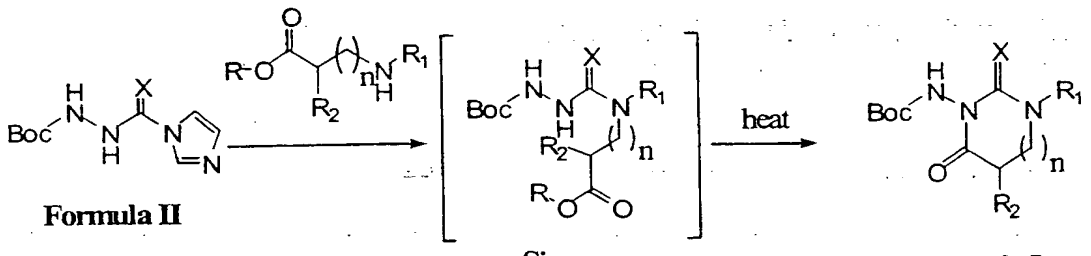
Carbamic acid, [tetrahydro-2,6-dioxo-3-[1-(phenylmethyl)-4-piperidinyl]-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester.



Solution-Phase Process for Making Compounds According to Formula I

In one embodiment, the present invention provides a one-pot solution-phase process for preparing compounds according to **Formula I** above depicted below as **Scheme I**. The process depicted below in **Scheme I** requires no chromatographies (for n = 0) and a simple liquid/liquid extraction and crystallization/filtration at the end.

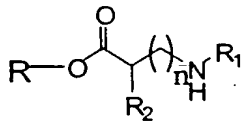
Scheme 1



The process depicted above in **Scheme I** begins with providing a compound according to **Formula II.** In **Formula II**, X is as defined above for **Formula I**. Compounds according to **Formula II** can be made from known starting materials and methods known to one of ordinary skill in the art. One particularly preferred method for the preparation of compounds according to **Formula II** involves slow addition of

commercially available *t*-butoxycarbonyl (Boc) hydrazine to carbonyldiimidazole (X = O) or thiocarbonyldiimidazole (X = S). Once made, compounds according to **Formula II** need not be isolated, but rather can be reacted *in situ* for the next step.

Compounds according to **Formula II** are first reacted with or amino acid esters having the following general structure:

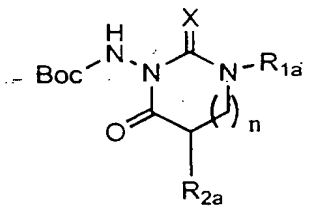


wherein R_1 and R_2 are as defined above for **Formula I**, and R is alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring. Preferred R is methyl, ethyl, and benzyl. These or amino acid esters are commercially available or are made from commercially available starting materials from methods known to one of ordinary skill in the art.

The resulting intermediates according to **Sia** need not be isolated, but rather undergo intramolecular cyclization to the desired products of **Formula I** on warming. Thus, the next step in the process is heating the reaction mixture. The preferred reaction time is 8 hours and the reaction temperature is preferably kept between 60-70°C for 3-aminohydantoin derivatives (**Formula I** wherein n = 0). The preferred reaction time is >24 hours and the reaction temperature is preferably kept between 100-110°C for 3-aminodihydrouracil derivatives (**Formula I** wherein n = 1). Commonly used organic solvents are used. Preferred organic solvents include THF, DMF, dioxane, and methylene chloride. The most preferred organic solvent is dioxane.

Solid-Phase Process for Making Compounds According to Formula I

In another embodiment, the present invention provides a solid-phase process for preparing compounds according to **Formula Ia below. Formula Ia** is a subset of **Formula I** compounds.



wherein

X is O or S;

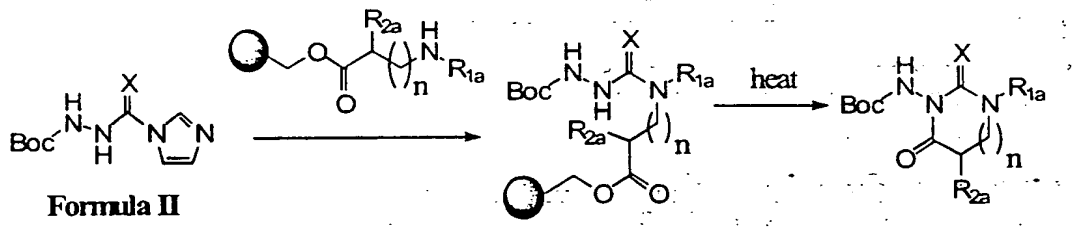
n is 0 or 1;

R_{1a} is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;

R_{2a} is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;

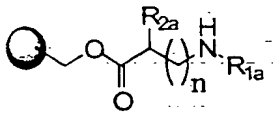
The solid phase process is depicted below as **Scheme II**.

Scheme II



Formula II **Siia** **Formula I**

The process depicted above in **Scheme II** begins with providing a compound according to **Formula II**. Compounds according to **Formula II** are first reacted with resin-bound or amino acid esters having the following general structure:



wherein R_{1a} and R_{2a} are as defined above for **Formula I**, and ○ is a Merrifield resin, hydroxymethyl resin, Wang resin, or PEG resin, preferably a Merrifield resin. These resin-bound or amino acid esters are made from commercially available starting materials from methods known to one of ordinary skill in the art. A preferred method for the preparation of Merrifield resin-bound or amino acid esters resins is to esterify the Merrifield resin with α-bromoacetic acid or acrylic acid. Relevant references include: Wilson, L. J.; Li, M.; Portlock, D. E. *Tetrahedron Lett.* **1998**, 39 5135-5138. Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, 37 3209-3212. Kolodziej, S.; Hamper, B. C. . *Tetrahedron Lett.* **1996**, 37 5277-5280.

Compounds according to **Formula II** are preferably reacted with these resin-bound or amino acid esters at room temperature. Intermediates according to **Siia** are

then thoroughly washed to remove impurities and excess reagents. In this reaction step, common organic solvents are used. Preferred organic solvents include THF, DMF, dioxane, acetonitrile and methylene chloride. The most preferred solvent is anhydrous DMF.

Warming compounds according to **Siia** induces intramolecular cyclization and release from the resin to provide the desired products according to **Formula I**. Thus, the next step in the process is heating the reaction mixture. The temperature of the cyclization reaction is preferably kept between about 60-70°C and the reaction time is preferably about 8-10 hours for the formation of 3-aminohydantoin derivatives (**Formula I**, wherein n = 0). The temperature of the cyclization reaction is preferably kept between about 90-95°C and the reaction time is preferably 24 hours for the formation of 3-aminodihydrouracil derivatives (**Formula I**, wherein n = 1).

This method allows for the ready preparation of 3-aminohydantoins/ thiohydantoins and 3-aminodihydrouracils/dihydrothiouracils which contain a wide variety of substituents at *N*-1, including basic groups which can be difficult to purify when made by solution methods.

The following non-limiting examples illustrate the present invention:

Example 1

Preparation of carbamic acid, [5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

To a solution of 990 mg (90%, 5.0 mmol) of thiocarbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-benzylglycine ethyl ester 996 mg (5 mmol). The resulting mixture is heated to 60 °C for 4 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (150 mL) and washed with water (2 x 50 mL), 0.1N aqueous HCl (2 x 50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford carbamic acid, [5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester (1.52 g, 95%).

Example 2

Preparation of carbamic acid, [4-methyl-5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

To a solution of 593 mg (90%, 3.0 mmol) of thiocarbonyldiimidazole in 15 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-

dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-benzylalanine ethyl ester 621 mg (3 mmol). The resulting mixture is heated to 60 °C for 4 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford carbamic acid, [4-methyl-5-oxo-3-(phenylmethyl)-2-thioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester (887 mg, 80%).

Example 3

Preparation of carbamic acid, (Tetrahydro-5,7-dioxoimidazol[5,1-b]thiazo- 6(5*H*)-yl)-, 1,1-dimethylethyl ester:

To a solution of 1.03 g (6.4 mmol) of carbonyldiimidazole in 30 mL of THF is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 10 mL of THF. The solution is stirred for 4 hours at room temperature, followed by the addition of methyl thiozolidine-2-carboxlate HCl salt 920 mg (5.0 mmol). The resulting mixture is heated to reflux for 4 hours. The THF is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (100 mL), 0.1N aqueous HCl (100 mL), water (100 mL), dried with Na_2SO_4 and concentrated *in vacuo* to afford carbamic acid, ((7aS)-tetrahydro-5,7-dioxoimidazol[5,1-b]thiazo- 6(5*H*)-yl)-, 1,1-dimethylethyl ester (1.0 g, 74%).

Example 4

Preparation of carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1,3-dioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester:

To a solution of 1.06 g (6.5 mmol) of carbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of benzyl (S)-(-) 1,2,3,4-tetrahydro-3-isoquinoline carboxylate p-toluenesulfonic acid salt 2.19 g (5 mmol) and triethylamine (0.5 mL). The resulting mixture is heated to 60 °C for 4 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (150 mL) and washed with water (2 x 50 mL), 0.1N aqueous HCl (2 x 50 mL), dried with $MgSO_4$ and concentrated to 20mL *in vacuo* to give a white precipitate. The solid is filtered off and dried in *vacuo* to afford carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1,3-dioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester (1.38 g, 87%).

Example 5

Preparation of carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1-oxo-3-thioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester:

To a solution of 972 mg (6 mmol) of carbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of benzyl (S)-(-) 1,2,3,4-tetrahydro-3-isoquinoline carboxylate p-toluenesulfonic acid salt 2.19 g (5 mmol) and triethylamine (0.5 mL). The resulting mixture is heated to 60 °C for 4 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (150 mL) and washed with water (2 x 50 mL), 0.1N aqueous HCl (2 x 50 mL), dried with $MgSO_4$ and concentrated to 20mL *in vacuo* to give a white precipitate. The solid is filtered off and dried in *vacuo* to afford carbamic acid, ((10aS)-1,5,10,10a-tetrahydro-1-oxo-3-thioxoimidazol[1,5-b]isoquinolin-2(3*H*)-yl)-, 1,1-dimethylethyl ester (1.56 g, 94%).

Example 6

Preparation of carbamic acid, (2,5-dioxo-3-phenyl-1-imidazolidinyl)-, 1,1-dimethylethyl ester:

To a solution of 915 mg (5.6 mmol) of carbonyldiimidazole in 15 mL of 1,4-dioxane is added dropwise 528 g (4.8 mmol) of *tert*-butyl carbazate in 15 mL of 1,4-dioxane. The solution is stirred for 2 hours at room temperature, followed by the addition of N-phenyl glycinate ethyl ester 716 mg (4.0 mmol). The resulting mixture is heated to 70 °C for 7 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 50 mL), dried with $MgSO_4$ and concentrated to 20mL *in vacuo* to give a white precipitate. The solid is filtered off and dried in *vacuo* to afford Preparation of carbamic acid, (2,5-dioxo-3-phenyl-1-imidazolidinyl)-, 1,1-dimethylethyl ester (858 mg, 76%).

Example 7

Preparation of carbamic acid, (5-oxo-3-phenyl-2-thioxo-1-imidazolidinyl)-, 1,1-dimethylethyl ester:

To a solution of 593 mg (3.0 mmol) of thiocarbonyldiimidazole in 15 mL of 1,4-dioxane is added dropwise 396 g (3.0 mmol) of *tert*-butyl carbazate in 15 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of N-phenyl glycinate ethyl ester 495 mg (3.0 mmol). The resulting mixture is heated to 70 °C for 7 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 50

mL), dried with $MgSO_4$ and concentrated to afford crude product which is further purified by Biotage column (eluent: EtOAc/Hexane, 3/7). The pure product, carbamic acid, (5-dioxo-3-phenyl-2-thioxo-1-imidazolidinyl)-, 1,1-dimethylethyl ester, is obtained as semisolid material (820 mg, 81%).

Example 8

Preparation of carbamic acid, (hexahydro-1,3-dioxoimidazol[1,5-a]pyridin-2(3*H*)-yl)-, 1,1-dimethylethyl ester:

To a solution of 972 mg (6 mmol) of carbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 792 g (6 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 2 hours at room temperature, followed by the addition of ethyl pipercolinate 785 mg (5 mmol). The resulting mixture is heated to 60-70 °C for 4 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (150 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 50 mL), dried with $MgSO_4$ and concentrated to afford carbamic acid, (hexahydro-1,3-dioxoimidazol[1,5-a]pyridin-2(3*H*)-yl)-, 1,1-dimethylethyl ester (1.21 g, 90%).

Example 9

Preparation of carbamic acid, (3-(phenylmethyl)tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 1.14 g (7 mmol) of carbonyldiimidazole in 50 mL of 1,4-dioxane is added dropwise 793 mg (6 mmol) of *tert*-butyl carbazate in 10 mL of 1,4-dioxane. The solution is stirred for 4 hours at room temperature, followed by the addition of *N*-benzyl--alanine ethyl ester 1.04 g (5 mmol). The resulting mixture is refluxed for 72 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc, washed with H_2O, 0.1 N HCl, H_2O respectively and dried over Na_2SO_4 and concentrated *in vacuo* to afford carbamic acid, (3-(phenylmethyl)tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (1.02 g, 64%).

Example 10

Preparation of carbamic acid, (3-(2-furanylmethyl)tetrahydro-2-oxo-6-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 988 mg (90%, 5.5 mmol) of thiocarbonyldiimidazole in 15 mL of 1,4-dioxane is added dropwise 660 mg (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-2-furanylmethyl- -alanine ethyl ester 985 mg (5 mmol). The resulting mixture is

refluxed for 24 hours. The dioxane is removed under reduced pressure. The residue is purified by Biotage column (eluent: EtOAc/Hexane, 6/4) to afford carbamic acid, (3-(2-furanylmethyl)tetrahydro-2-oxo-6-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (1.25 g, 77%).

Example 11

Preparation of carbamic acid, (3-(2-furanylmethyl)tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 810 mg (90%, 5.0 mmol) of carbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 660 mg (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-2-furanylmethyl -alanine ethyl ester 985 mg (5 mmol). The resulting mixture is refluxed for 24 hours. The dioxane is removed under reduced pressure. The residue is purified by Biotage column (eluent: EtOAc/Hexane, 6/4) to afford carbamic acid, (3-(2-furanylmethyl)tetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (1.01 g, 65%).

Example 12

Preparation of carbamic acid, (3-butyltetrahydro-6-oxo-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 984 mg (90%, 5.5mmol) of thiocarbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-n-butyl- -alanine methyl ester 795 mg (5 mmol). The resulting mixture is refluxed for 24 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford carbamic acid, (3-butyltetrahydro-6-oxo-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (1.23 g, 81%).

Example 13

Preparation of carbamic acid, (3-butyltetrahydro-2,6-dioxo -1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 1.14 g (7.0 mmol) of carbonyldiimidazole in 30 mL of 1,4-dioxane is added dropwise 0.79 g (6 mmol) of *tert*-butyl carbazate in 20 mL of 1,4-dioxane. The solution is stirred for 4 hours at room temperature, followed by the addition

of *N*-n-butyl- -alanine methyl ester 795 mg (5 mmol). The resulting mixture is refluxed for 40 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc, washed with H_2O, 0.1 N HCl, H_2O respectively and dried over Na_2SO_4 and concentrated *in vacuo* to afford carbamic acid, (3-butyltetrahydro-2,6-dioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (1.28 g, 84%).

Example 14

Preparation of carbamic acid, (tetrahydro-6-oxo-3-(4-methoxyphenyl)-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester:

To a solution of 988 mg (90%, 5.5 mmol) of thiocarbonyldiimidazole in 25 mL of 1,4-dioxane is added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate in 25 mL of 1,4-dioxane. The solution is stirred for 3 hours at room temperature, followed by the addition of *N*-(4-methoxyphenyl)- -alanine ethyl ester 1.12 g (5 mmol). The resulting mixture is refluxed for 48 hours. The dioxane is removed under reduced pressure. The residue is dissolved in EtOAc (100 mL) and washed with water (50 mL), 0.1N aqueous HCl (2 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford carbamic acid, (tetrahydro-6-oxo-3-(4-methoxyphenyl)-2-thioxo-1(2*H*)-pyrimidinyl)-, 1,1-dimethylethyl ester (0.59 g, 33%).

Example 15

Preparation of Merrifield resin-bound -bromoacetate ester :

To a solution of DIC (diisopropylcarbodiimide) (31g, 253 mmol), -bromoacetic acid (35g, 246 mmol) and Merrifield resin (50 g, 33.5 mmol, loading level: 0.67 mmol/g) in methylene chloride (600 mL) is added DMAP (1g, 8.1 mmol). The resulting mixture is shaken at room temperature for 24 hours. Resin is collected on a glass filter and washed two times each with DMF, MeOH, DCM. The resin is dried to give the Merrifield resin-bound -bromoacetate ester (53.1 g, yield 98%).

Example 16

Preparation of carbamic acid, [2,5-dioxo-3-[2-(2-pyridinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound -bromoacetate ester (2 g, loading 0.67 mmol/g) is treated with DMF (40 mL) and 2-(2-aminoethyl)pyridine (810 mg, 6.6 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM afforded resin. This is then treated with Boc-hydrazinecarbonylimidazole

(6.6 mmol) in 40 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-(2-pyridinyl)ethyl). The resin is then placed in a flask with 40 mL of DMF and heated to 65-70°C for 8 hours. After cooling, the resin is filtered, washed with small amount of DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product, carbamic acid, [2,5 dioxo-3-[2-(2-pyridinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester (183 mg, 63%).

Example 17

Preparation of carbamic acid, [3-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound -bromoacetate ester (2 g, loading 0.67 mmol/g) is treated with DMSO (60 mL) and 5-methoxytryptamine (1.0 g, 5.26 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (5.2 mmol) in 60 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-(5-methoxy-1*H*-indol-3-yl)ethyl). The resin is then placed in a flask with 50 mL of DMF and heated to 60-70°C for 8 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product, carbamic acid, [3-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester (310 mg, 61%).

Example 18

Preparation of carbamic acid, [3-[2-(1*H*-imidazol-4-yl)-ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound -bromoacetate ester (2 g, loading 0.67 mmol/g) is treated with DMSO (60 mL) and histamine (733 mg, 6.6 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM afford the resin. This is then treated with Boc-hydrazinecarbonylimidazole (6.6 mmol) in 60 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times

each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-(1*H*-imidazol-4-yl)-ethyl). The resin is then placed in a flask with 50 mL of DMF and heated to 60-70°C for 8 hours. After cooling, the resin is filtered, washed with small amount of DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product, carbamic acid, [3-[2-(1*H*-imidazol-4-yl)-ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester (202 mg, 50%).

Example 19

Preparation of carbamic acid, [3-[2-(1-methyl-2-pyrrolidinyl)ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

The Merrifield resin-bound -bromoacetate ester (3 g, loading 0.67 mmol/g) is treated with DMSO (60 mL) and 2-(2-aminoethyl)-1-methylpyrrolidine (1.42 g, 10 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (10 mmol) in 60 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-(1-methyl-2-pyrrolidinyl)ethyl). The resin is then placed in a flask with 50 mL of DMF and heated to 60-70°C for 8 hours. After cooling, the resin is filtered, washed with small amount of DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product (445 mg, 69%).

Example 20

Preparation of carbamic acid, [3-[2-[[5-nitro-2-pyridinyl]amino]ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound -bromoacetate ester (3 g, loading 0.67 mmol/g) is treated with DMSO (60 mL) and 2-(2-aminoethylamino)-5-nitropyridine (1.82 g, 10 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (10 mmol) in 60 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-[[5-nitro-2-pyridinyl]amino]ethyl). The resin is then placed in a flask with 50 mL of DMF and heated to 60-70°C for 8 hours. After cooling, the resin

is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product, carbamic acid, [3-[2-[[5-nitro-2-pyridinyl]amino]ethyl]-2,5-dioxo-1-imidazolidinyl]-, 1,1-dimethylethyl ester (440 mg, 58.5%).

Example 21

Preparation of carbamic acid, [2,5-dioxo-3-[2-(1-piperidinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound -bromoacetate ester (2 g, loading 0.67 mmol/g) is treated with DMSO (60 mL) and 1-(2-aminoethyl)piperidine (0.88 g, 6.7 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (6.5 mmol) in 50 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 10 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 0, X = O, R_1 = 2-(1-piperidinyl)ethyl). The resin is then placed in a flask with 30 mL of DMF and heated to 60-70°C for 8 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product, carbamic acid, [2,5-dioxo-3-[2-(1-piperidinyl)ethyl]-1-imidazolidinyl]-, 1,1-dimethylethyl ester (262 mg, 59%).

Example 22

Preparation of Merrifield resin-bound acrylate ester:

To a solution of DIC (15g, 119 mmol), acrylic acid (17g, 208 mmol) and Merrifield resin (25 g, 200 mmol, loading level: 0.80 mmol/g) in methylene chloride (300 mL) is added DMAP (0.5g, 4 mmol). The resulting mixture is shaken at room temperature for 24 hours. Resin is collected on a glass filter and washed two times each with DMF, MeOH, DCM. The resin is dried to give the Merrifield resin-bound acrylate ester (37 g, yield 94%).

Example 23

Preparation of carbamic acid, [tetrahydro-3-[(5-nitro-2-pyridinyl)amino]ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound acrylate ester (2 g, loading 0.8 mmol/g) is treated with DMSO (50 mL) and 2-(2-aminoethylamino)-5-nitropyridine (1.46 g, 8.0 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (8 mmol) in 40 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 24 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 1, X = O, R_1 = (5-nitro-2-pyridinyl)aminoethyl). The resin is then placed in a flask with 40 mL of DMF and heated to 95°C for 24 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 40 mL of EtOAc and filtered, concentrated *in vacuo* to give desired product carbamic acid, [tetrahydro-3-[(5-nitro-2-pyridinyl)amino]ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester (289 mg, 46%).

Example 24

Preparation of carbamic acid, [tetrahydro-3-[2-(4-morpholinyl)ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound acrylate ester (2 g, loading, 8.0 mmol/g) is treated with DMSO (50 mL) and 4-(2-aminoethyl)morpholine (1.04 g, 8 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (8 mmol) in 40 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 24 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 1, X = O, R_1 = 2-(4-morpholinyl)ethyl). The resin is then placed in a flask with 40 mL of DMF and heated to 95°C for 24 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 40 mL of EtOAc and filtered, concentrated *in vacuo* to give desired product carbamic acid, [tetrahydro-3-[2-(4-morpholinyl)ethyl]-2,6-dioxo-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester (229 mg, 42%).

Example 25

Preparation of carbamic acid, [tetrahydro-2,6-dioxo-3-[1-(phenylmethyl)-4-piperidinyl]-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound acrylate ester (2 g, loading, 8.0 mmol/g) is treated with DMSO (50 mL) and 4-amino-1-benzyl-piperidine (1.52 g, 8 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (8 mmol) in 40 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 24 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 1, X = O, R_1 = 1-(phenylmethyl)-4-piperidinyl). The resin is then placed in a flask with 40 mL of DMF and heated to 95°C for 24 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 20-30 mL of MeOH and filtered, concentrated *in vacuo* to give desired product carbamic acid, [tetrahydro-2,6-dioxo-3-[1-(phenylmethyl)-4-piperidinyl]-1(2*H*)-pyrimidinyl]-, 1,1-dimethylethyl ester (289 mg, 45%).

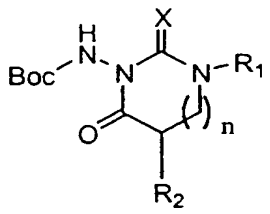
Example 26

Preparation of carbamic acid, [tetrahydro-6-oxo-3-(phenylmethyl)-2-thioxo-1(2*H*) -pyrimidinyl]-, 1,1-dimethylethyl ester:

Merrifield resin-bound acrylate ester (2 g, loading, 8.0 mmol/g) is treated with DMSO (50 mL) and benzyl amine (1.025 g, 9 mmol) and allowed to shake for 24 hours at room temperature. Washing two times each with DMF, MeOH, DCM affords the resin. This is then treated with Boc-hydrazinecarbonylimidazole (6 mmol) in 50 mL of DMF (prepared *in situ* according to the process of solution-phase chemistry which is described above in **Scheme 1**) at room temperature for 24 hours and washed two times each with DMF, MeOH, DCM to afford a resin according to **Siia** (where n = 1, X = S, R_1 = benzyl). The resin is then placed in a flask with 50 mL of DMF and heated to 95°C for 24 hours. After cooling, the resin is filtered, washed two times each with DMF, DCM and MeOH and the combined filtrates concentrated. The residue is dissolved in 40 mL of EtOAc and filtered, concentrated *in vacuo* to give desired product carbamic acid, [tetrahydro-6-oxo-3-(phenylmethyl)-2-thioxo-1(2*H*) -pyrimidinyl]-, 1,1-dimethylethyl ester (117 mg, 22%).

WHAT IS CLAIMED IS:

1. A method for making a compound according having the following structure:



wherein

X is O or S;

n is 0 or 1;

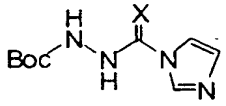
R_1 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;

R_2 is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring; and

when n is 0, R_1 and R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring; or when n is 1, R_1 and the member carbon atom adjacent to the carbon atom containing R_2 may instead together form a ring system; said ring system being carbocyclic ring, heterocyclic ring, or heteroaromatic ring;

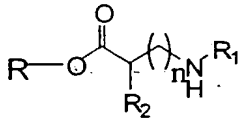
said method comprising the steps of:

a) providing a compound having the following structure



wherein X is as defined above;

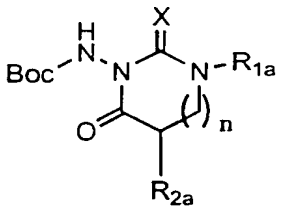
b) reacting the compound provided in step a above with an or amino acid ester having the structure:



wherein R_1 and R_2 are as defined above and R is alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring; and

c) heating the reaction mixture.

2. A method for making a compound according having the following structure:



wherein

X is O or S;

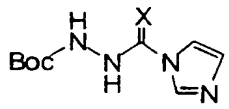
n is 0 or 1;

R_{1a} is H, alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;

R_{2a} is H, C_1-C_8 alkyl, carbocyclic ring, heterocyclic ring, aromatic ring, or heteroaromatic ring;

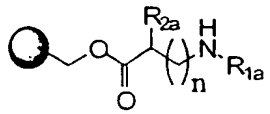
said method comprising the steps of:

a) providing a compound having the following structure



wherein X is as defined above;

b) reacting the compound provided in step a above with a resin-bound or amino acid ester having the structure:



wherein R_1 and R_2 are as defined above and  is a Merrifield resin, hydroxymethyl resin, Wang resin, or PEG resin; and

c) heating the reaction mixture.